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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/044,310	01/11/2002	Rajendra Singh	SURR.85	6784

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EXAMINER	
GAKH, YELENA G	

ART UNIT	PAPER NUMBER
1743	

DATE MAILED: 11/10/2003

19

Please find below and/or attached an Office communication concerning this application or proceeding.

CLO-16

Office Action Summary	Application No.	Applicant(s)	
	10/044,310	SINGH ET AL.	
	Examiner	Art Unit	
	Yelena G. Gakh, Ph.D.	1743	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,6-9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim Objections

1. Claim 8 is objected to because of the following informalities: "*approximately* most different" is a technically incorrect expression, since it combines a definite adjective "most" with an indefinite adjective "approximately". Appropriate correction is required.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 9 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for MS^4 mass spectra, does not reasonably provide enablement for MS^2 and MS^3 mass spectra. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The specification explicitly discloses, "the MS^2 spectra and MS^3 spectra were essentially identical for the two species [PGD_2 and PGE_2] at all ionization energies" (page 6, lines 31-32), which makes it impossible for any routineer in the art to distinguish MS^2 and MS^3 spectra of PGD_2 and PGE_2 at any energy and therefore to perform the method recited in claim 9.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. **Claims 1-4** are rejected under 35 U.S.C. 103(a) as being unpatentable over Newby (Rap. Com. Mass Spectr., 1997) in view of Schilling et al. (Biomed. Environ. Mass Spectr., 1986).

Newby discloses "rapid simultaneous analysis of prostaglandin E_2, 12-hydroxy-eicosatetraenoic acid and arachidonic acid using high performance liquid chromatography/ electrospray ionization [ESI] mass spectrometry" emphasizing that "the advantages of this method include minimal sample preparation and elimination of the problem associated with thermal stability for GC/MS analysis" (Abstract). HPLC is performed in acidic media (acetonitrile with aqueous formic acid, page 1725).

Newman does not teach his method for analysis of a mixture of at least two prostaglandins, PGE_2 and PGD_2 in particular, with adding a basic solution to the HPLC eluent.

Schilling discloses "ammonia (NH_3 and N_2H_3) direct chemical ionization mass spectrometry of underivatized prostaglandin-H_2 and other selected stable prostaglandins", including intact PGH_2 and its stable PGE_2 and PGD_2 isomers, emphasizing that the "reagent gas [NH_3] clearly distinguished between several arachidonic acid metabolites, differing in their number of exchangeable protons. ... Consequently, it would appear that negative and positive

ion, NH_3 (N_2H_3) direct chemical ionization mass spectrometry would be useful in the analysis of labile arachidonic acid metabolites, without the need for prior derivatization" (Abstract).

It would have been obvious for anyone of ordinary skill in the art to modify and expand Newby's method for analysis of a mixture containing more than one prostaglandin by adding ammonia hydroxide to the eluent, because Schilling demonstrated that performing MS analysis in the atmosphere of NH_3 allows detecting prostaglandin isomers, including PGE_2 and PGD_2, without their prior derivatization. Adding basic NH_4OH solution to the HPLC eluent prior to MS analysis is similar to adding NH_3 gas to the mixture in Schilling's method.

8. **Claim 5** is rejected under 35 U.S.C. 103(a) as being unpatentable over Newby and Schilling, as applied to claims 1-4 above, and further in view of Margalit et al. (Anal. Biochem., 1996).

Newby in view of Schilling do not particularly disclose tandem mass spectrometry for analysis of prostaglandins.

Margalit discloses "the development of a new method for eicosanoid assessment in biological samples by electrospray and tandem mass spectrometry (MS/MS) in the multiple reaction monitoring" with detecting PGE_2 as the most abundant metabolite, and PGE_1, PGD_2 and PGF_2-α as minor components.

It would have been obvious for anyone of ordinary skill in the art to use tandem MS/MS spectrometry, disclosed by Margalit, in Newby-Schilling's method, because Margalit demonstrated advantages of ESI-MS/MS spectrometry in detection of prostaglandin metabolites.

9. **Claim 6** is rejected under 35 U.S.C. 103(a) as being unpatentable over Newby, Schilling and Margalit, as applied to claims 1-5 above, and further in view of Ballard et al. (Rap. Comm. Mass Spectr., 1992) or Kanai et al. (Kuromatogurafi, 1996).

Newby in view of Schilling and Margalit do not teach MS^4 tandem mass spectrometry.

Ballard and Kanai disclose instrumental improvements of MS spectrometers, which give an opportunity to perform more informative MS^3 and MS^4 experiments, which are "very useful for the structural analysis of biomolecules" (Kanai, Abstract).

It would have been obvious for anyone of ordinary skill in the art to apply improved and more sophisticated MS^4 experiments for analysis of prostaglandins, because MS^4 spectra are highly informative for biomolecules, as indicated by Kanai.

10. **Claims 7-8** are rejected under 35 U.S.C. 103(a) as being unpatentable over Margalit in view of Bomse et al. (US 5,015,848).

Margalit discloses "the development of a new method for eicosanoid assessment in biological samples by electrospray and tandem mass spectrometry (MS/MS) in the multiple reaction monitoring" with detecting PGE_2 as the most abundant metabolite, and PGE_1, PGD_2 and PGF_2-α as minor components.

Margalit does not particularly teach varying ionization energy to achieve significant or the largest difference between mass spectra of at least two prostaglandin isomers.

Bomse teaches a method for analyzing a mixture by tandem mass spectrometry varying ionization energy and obtaining a series of spectra with different ionization energies in order to identify components of the mixture.

It would have been obvious for anyone of ordinary skill in the art to modify Margalit's MS/MS method of analysis of prostaglandins using variable ionization energy, as taught by Bomse, because this allows better resolution of mass spectra due to different modes of ionization of different components in the mixture and because it is possible to achieve the largest difference between mass spectra of the components using this method.

11. **Claims 10** is rejected under 35 U.S.C. 103(a) as being unpatentable over Margalit and Bomse, as applied to claims 7-8 above, and further in view of Ballard or Kanai.

Margalit in view of Bomse do not disclose MS^4 tandem MS.

Ballard and Kanai disclose instrumental improvements MS spectrometers, which give an opportunity to perform more informative MS3 and MS4 experiments, with such characteristic "very useful for the structural analysis of biomolecules" (Kanai, Abstract).

It would have been obvious for anyone of ordinary skill in the art to modify Margalit - Bomse method by performing MS^4 spectrometry, as taught by Ballard or Kanai, because such spectrometry provides more structural information for biomolecules, as indicated by Kanai.

Conclusion

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Bose et al. (Anal. Biochem., 1978) teach "mass spectral studies. VIII. Some aspects of chemical ionization mass spectroscopy using ammonia as reagent gas: a valuable technique for biomedical and natural products studies"; *Traitler et al. (Colloq., 1987)* discloses GS/MS analysis of prostanoids (prostaglandins) with their preliminary separation by liquid chromatography in acidic media (elution over acidic silica gel) (Abstract); *Strife et al. (Rapid Commu. Mass Spectr.)* discloses GC/MS/MS spectrometry of prostaglandins using ammonia-CI source in the first MS stage.

The closest art that is not prior to this application is *Takabatake et al. (Prostaglandins, ...,2002)* disclosing "simultaneous quantification of prostaglandins in human synovial cell-cultured medium using liquid chromatography/tandem mass spectrometry"; *Yang et al. (Anal. Biochem., 2002)* teach "quantitative high-performance liquid chromatography/ electrospray ionization tandem mass spectrometric analysis of 2- and 3-series prostaglandins in cultured tumor cells".

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (703) 306-5906. The examiner can normally be reached on 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill A. Warden can be reached on (703) 308-4037. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0661.

Yelena G. Gakh
10/30/03

Yelena Gakh